

Mortality in end-stage renal disease: the importance of the genetic background

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In the current issue of the *Polish Archives of Internal Medicine*, Świderska et al.¹ reports on genetic variants of certain cytokines and vitamin D pathway in dialyzed patients with end-stage renal disease (ESRD). ESRD is a permanent kidney failure, the endpoint of chronic kidney disease (CKD), frequently caused by diabetes mellitus or arterial hypertension but also by other nephropathies. Recently, Mills et al.² estimated a global burden of 497 million adults with CKD (stages 1–5), with age-specific prevalence of stages 3–4 reaching 15.8% among men and 22.0% among women older than 70 years. Mortality rates in patients with ESRD, especially those with diabetes, are high, approaching 10% per year.

Deficiency of active vitamin D was reported to be an independent predictor of mortality in dialyzed patients with diabetes (hazard ratio [HR], 1.71; 95% confidence interval [CI], 1.21–2.43) during a 3-year prospective study.³ In another report⁴ on the ESRD cohort described by Świderska et al.,¹ the common variants of vitamin D-binding protein (group-specific component – GC), vitamin D receptor, and retinoic-acid receptor α (RXR α) were not associated with the mortality rate in dialyzed patients. Because active vitamin D was measured in the study subgroup as 25(OH)D in a randomly selected fraction of patients,⁴ it could be concluded that vitamin D deficiency was the culprit rather than the genetic variants of the vitamin pathway. In fact, a more detailed analysis within the same ESRD cohort⁵ revealed that GC rs7041 TT homozygotes had lower 25(OH)D levels than rs7041 GG homozygotes, but no clinical variables were associated with this polymorphism. Thus, in summary, an environmental factor, namely, active vitamin D deficiency, is an independent predictor of mortality in ESRD, while genetic variants in the vitamin D pathway have no effect on clinical outcomes.

Even more interesting is a novel finding by Świderska et al.¹ that a common missense interleukin 13 (IL-13) arginine 130 to glutamine

variant can predict mortality in dialyzed patients. ESRD patients with a less frequent glutamine variant (rs20541 T carriers) had increased mortality rates in comparison with IL-13 arginine 130 homozygous subjects. This difference was significant (HR, 1.28; CI, 1.01–1.63) and independent of older age at first dialysis, presence of coronary artery disease, and other predictors.

The genetic variants of IL-13 were studied thoroughly in allergic disorders. This single nucleotide polymorphism (SNP) was associated with allergic rhinitis in numerous studies⁶ and a functional analysis demonstrated an increased activity of the glutamine variant on the IL-13 receptor activation, as measured by signal transducer and activator of transcription 6 (STAT6) phosphorylation.⁷ However, functional effects of IL-13 on renal disease progression or comorbidities of ESRD have been studied only recently. In the animal model, overexpression of IL-13 protected the kidneys against acute ischemia–reperfusion injury and was suggested to be beneficial for kidney transplant protection.⁸ However, fibrotic kidneys have massive CD4⁺ lymphocyte infiltrates and adoptive transfer of CD4⁺ helper lymphocytes accelerated in progression of tubulointerstitial fibrosis mouse model, depending on Th₂ cells secreting IL-4 and IL-13.⁹ Bone marrow-derived precursors of fibroblasts are among target cells for IL-13-mediated activation. These cells contribute to renal fibrosis and respond to IL-13 with STAT6 phosphorylation. Moreover, experimental knockout of STAT6 decreased interstitial fibrosis of the kidneys.¹⁰ However, the question of how IL-13 can modify the mortality rate in ESRD patients whose kidneys were already damaged requires elucidation.

In the past, there were some experimental studies on the adverse effects of IL-13 (or other Th₂-like cytokines) on the cardiovascular system. In vitro, IL-13 induced apoptosis of human coronary arterial endothelial cells, an effect which was mediated again by STAT6 phosphorylation

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and accompanied by a decrease in the production of vascular endothelial growth factor.¹¹ However, IL-13 variants were not found to be associated with cardiovascular phenotypes. Patients' data reported by Świdarska et al.¹ did not explain how increased activity of the glutamine variant translated into comorbidities or causes of death in ESRD patients. The analysis of subjects with ESRD and diabetes only did not reveal such a risk of rs20541.⁴ Considering a hypothetical link between IL-13, or in general, TH₂-like cytokines and increased mortality rate of dialyzed ESRD patients, one should remember about a wide spectrum of clinical conditions leading to progression of chronic kidney failure, but also about comorbidities including allergic disorders and altered drug pharmacokinetics and interactions in dialyzed patients.

Yet, there is another interesting finding in the study by Świdarska et al.,¹ focused on the variant of the gene for IL-28B (rs1279860). This polymorphism became well known due to its pharmacogenetic interaction with dual ribavirin-interferon therapy for chronic hepatitis C. IL-28B, also known as interferon-λ3, has lower expression at the presence of viral RNA in the most common rs1279860 CC homozygotes. But the cytokine level seems sufficient for inducing interferon-stimulated genes responsible for viral clearance. In our meta-analysis, Polish patients with chronic hepatitis C had increased frequency of rs1279860 CT or TT genotypes, suggesting that increasing T variant prevalence of SNP was due to a spontaneous virus clearance in rs1279860 CC homozygotes.¹² In ESRD patients, rs1279860 SNP TT homozygotes had an increased mortality rate but only if a history of hepatitis B or C virus infection was excluded. The cytokine is induced by viral infection in many tissues. It remains to be established whether overrepresentation of rs1279860 TT genotype among ESRD patients with coronary artery disease found by Świdarska et al.¹ had an effect on patients' survival rates because no association was present with myocardial infarction, one of the main death causes. Moreover, in a small prospective study, Roed et al.¹³ found several markers of coronary artery disease elevated in patients with chronic hepatitis C in comparison with controls.

In summary, the survival analysis is rather a rough method to evaluate contribution of genetic factors to the outcome of a disease, especially if there are many distinct clinical entities leading to the same endpoint as in ESRD. The study by Świdarska et al.¹ included more than 1000 patients with ESRD; therefore, it had adequate statistical power to exclude other candidate genes polymorphisms investigated. However, it will require more detailed clinical characteristics to identify the positive association signals for ESRD mortality found in *IL13* and *IL28B* genes.

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